The inv dup (15) or idic(15) syndrome: a case report.

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Abstract
This report describes a patient who presented with hypotonia and epileptic seizures. She was prenatally diagnosed as a supernumerary chromosome carrier. By means of Fluorescence in Situ Hybridization (FISH) using Vysis Prader-Willi/Angelman region probes, the marker chromosome was double positive for D15Z1 and quadruple positive for SNRPN. Her karyotype was thus interpreted as 47, XX,+ idic(15)(pter→q13::q13→ pter) .ish idic (15)(D15Z1++, SNRPN++++). No sphincters control and signs of kyphoscoliosis may provide additional evidence for the spectrum of clinical manifestations in the inv dup (15) syndrome to be broader than previously considered. The mother had a history of two miscarriages and one molar pregnancy, it suggests she could have been prone to unsuccessful meiosis. The existence of genetic or environmental factors predisposing to chromosomal aberrations and its correlation with the common instability of this chromosomal region are issues to be further investigated.

Keywords: Inverted duplication 15, isodicentric, marker chromosome, FISH.

Introduction

Distinctive clinical findings of the inv dup(15) or idic(15) (inverted duplication of proximal chromosome 15 or isodicentric 15 chromosome) syndrome are represented by early central hypotonia, developmental delay, intellectual disability, epilepsy and autistic behaviour. The latter is characterized by lack of social interaction, non-functional use of objects, primordial type of exploration, stereotypies, absent or very poor echolalic language, limited comprehension, and poor intention to communicate.[1]
The region 15q11q13 is known for its propensity to instability,[2-4] where many rearrangements may take place, like deletions (either associated with Angelman or Prader-Willi syndrome, depending on the parental origin), translocations, inversions and supernumerary marker chromosomes, formed by the inverted duplication of proximal 15 chromosome.
Two cytogenetic types of inv dup (15) marker chromosomes have been identified, with different phenotypic consequences.[5-8] The first one is a metacentric or submetacentric and heterochromatic chromosome, not containing the PWS/AS critical region. It may be familial or de novo and its cytogenetic description is dic(15)(q11).dic(15)(q11).
The second type of inv dup (15) has euchromatin, it includes the PWS/AS critical region.[9,10] The cytogenetic description is dic(15)(q12 or q13). The vast majority of dic(15)(q12 or q13) derives from the two homologous maternal chromosomes at meiosis, and is reportedly associated with an advanced maternal age at conception, similar to other aneuploides.[11]
Here, we describe a patient with a large inv dup (15) and some uncommon clinical findings.

Case report

A five year old female was born to a 36 year old mother and her 49 year old partner. There was no history of consanguinity. The mother had two miscarriages and one molar pregnancy prior to the birth of her child.
At a gestational age of 17 weeks an amniocentesis was performed and the cytogenetic prenatal diagnosis was carried out. The fetus was diagnosed as a supernumerary chromosome carrier (Fig. 1). Parental

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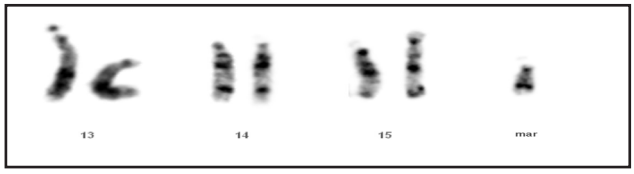
karyotyping was therefore performed and resulted normal in both cases. The FISH diagnosis was not available at that moment.

Fig. 1- G-banded partial karyotype of the girl, showing an additional marker chromosome



Cardiac, abdominal and limb malformations were ruled out through prenatal ultrasonographic examination. Genetic counselling was provided and reproductive options were discussed, the couple decided to continue to terminus.

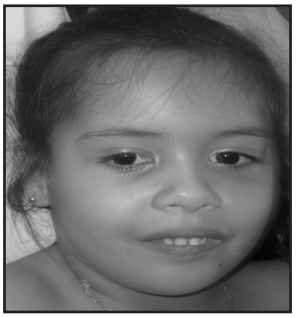
It was otherwise an uneventful pregnancy; the baby was born at term through a caesarean surgery with a low birth weight (2800 grams), and a length of 47cm.

Hypotonia was noted shortly after delivery, and seizures presented at two months of age with an abnormal electroencephalogram (EEG).

At a chronological age of seven months the physical examination revealed a developmental delay, depressed nasal bridge, epicanthic folds, short nose, anteverted nares, trident hairline, short neck, a hypopigmented patch located over the right paravertebral region in the back, a telangiectatic lesion of skin in the posterior region of the right shoulder, as well as a *cafe au lait* patch in the left paraumbilical area.

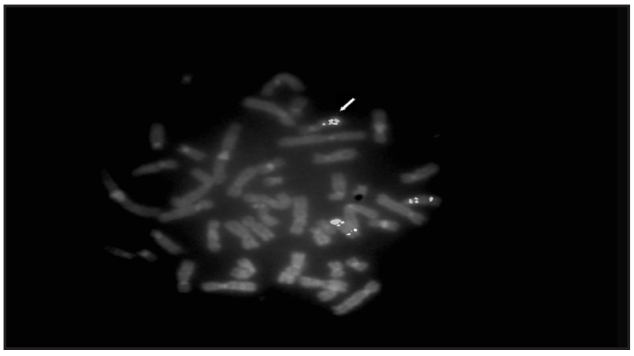
Currently, at a chronological age of 5 years (Fig. 2), she has a height of 107 centimetres (50-75th percentile), weight of 20 kilograms (75-90th percentile) and a head circumference of 49 centimetres (25-50th percentile). She shows speech delay, moderate mental retardation, autistic behaviour, no sphincters control and incipient signs of kyphoscoliosis.

Fig. 2- The patient at age 5 years old with depressed nasal bridge, epicanthic folds, short nose, anteverted nares.



Fluorescence in Situ Hybridization (FISH) was carried out using Vysis Prader- Willi/Angelman region probes that contains D15Z1 at the 15cen region (spectrum green), SNRPN at the 15q11- q13 PWS/AS critical region (spectrum orange) and PML at 15q22 (spectrum orange). The marker chromosome was double positive for D15Z1 and quadruple positive for SNRPN (Fig. 3). Her karyotype was thus interpreted as 47, XX,+ idic(15)(pter→q13::q13→ pter) .ish idic (15)(D15Z1++, SNRPN++++) (Fig. 3).

Fig. 3- Fluorescence in situ hybridization (FISH) analysis using Vysis PWS/AS region probe. The inv dup(15) chromosome (arrow) is double positive for D15Z1 (green), quadruple positive for SNRPN (orange).



Discussion

The patient here described has been affected with hypotonia, a developmental delay with moderate psychomotor retardation, epileptic seizures, as well as an autistic behaviour. She also presents a dysmorphic pattern. These are common findings in the individuals with an additional inv dup (15) chromosome containing the PW-AS critical region.[12]

Other phenotypic characteristics occasionally recognized by some authors [12,13] are also present in our patient; this is the case of skin areas with increased or reduced pigmentation.

Bataglia makes reference to 160 similar cases previously reported as affected with this syndrome. An attempt to establish a phenotype-genotype correlation has been made, but it resulted problematic. In fact, manifestations such as seizures history, behavior disorder, or developmental status are difficult to assess accurately, especially in young children, and there is also a considerable variation in the chromosomal breakpoints.[10]

To the best of our knowledge the kyphoscoliosis and the lack of control of the sphincters in our patient are clinical manifestations not previously reported.

This case may provide additional evidence for the spectrum of clinical manifestations to be broader than previously considered in cases with inv dup(15) or idic(15) syndrome.

The instability at the 15q11-q13 region is probably due to the presence of region-specific low-copy repeats.[14] This region is frequently involved in structural rearrangements such as deletions, duplications, triplications, and inverted duplications.[9]

Advanced maternal and paternal ages were both noted in this case. According to Battaglia et al. (2008) the inv dup (15), including the PWS/AS critical region, arises mainly from erroneous maternal meiosis in women with advanced maternal age at conception.[12] The fact that the mother had a history of two miscarriages and one molar pregnancy suggests she could have been prone to unsuccessful meiosis. Normal parental karyotyping also supports this idea.

Our patient comes from a province located at the eastern part of the country, where a founder effect seems to explain the high prevalence of rare diseases like Spinocerebellar Ataxia Type 2.[15] The existence of genetic or environmental factors predisposing to chromosomal aberrations and its correlation with the common instability of this chromosomal region are issues to be further investigated.

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